INFECTIOUS MONONUCLEOSIS COMPLICATED BY ACUTE HAEMOLYTIC ANAEMIA DUE TO ANTI-HI ANTIBODY

PIO MANGION,
M.D. M.R.C.P.(U.K.)

Medical Registrar, St. Peter's Hospital, Chertsey, Surrey, (now Medical Registrar, Charing Cross Group)

Significant anaemia is uncommon in infectious mononucleosis. When it occurs, it is usually due to increased red cell destruction though bone marrow hypoplasia may sometimes be responsible (Worlledge and Dacie, 1969). In the majority of studied cases, the temporary production of high thermal amplitude antibodies of i-specificity was apparently responsible for the haemolytic anaemia. A case of infectious mononucleosis complicated by a severe haemolytic anaemia due to a different antibody of HI-specificity is here described.

Case Report

A 25-year old man, manager of a grocery shop, was admitted to St. Peter's Hospital, Chertsey, Surrey, on 1st May, 1971, with a three-day history of intermittent generalised abdominal pain, persistent nausea and slight vomiting. He had felt feverish, very tired, and short of breath on the slightest exertion. He had noted that his skin had become increasingly pale, and that his urine was a dark red colour. There was no sore throat or skin rash. No relevant past history was obtained.

On examination, he was a thin, ill young man with marked pallor and moderate jaundice. His temperature was 38.6°C. He had a regular full pulse of 100 per minute and a blood pressure of 130/60. The only abnormality on examination of the heart was a soft midsystolic murmur

heard all over the praecordium. There were no abnormalities in the mouth, the fauces and the joints. Non-tender moderately enlarged lymph nodes were present in the neck, axillae and inguinal regions. Examination of the abdomen revealed a firm non-tender 4 cm splenomegaly but the liver was not palpable. There was no purpura or bone tenderness. The respiratory and neurological systems were normal.

Immediate investigations gave the following results:

Urine: reddish-brown colour, bilirubin absent, excess urobilinogen present, porphyrins absent; tests for haemoglobin were strongly positive.

Haemoglobin 8.5 g/100 ml, PCV 24%, MCHC 35%, reticulocytes 6%; white cell count 10,600 c.mm. with 56% neutrophils, 12% lymphocytes, 7% monocytes, 4% myelocytes, and 21% atypical mononuclear cells; platelet count 119,000/c. mm.; the blood smear showed increased polychromasia and some microspherocytes.

Serum bilirubin 5.2 mg/100 ml (unconjugated fraction 4.5 mg/100 ml), serum alkaline phosphatase 70 I.U./litre, serum aspartate aminotransferase 22 I.U./litre, serum hydroxybutyrate dehydrogenase 350 I.U./litre.

Blood urea 80 mg/100 ml, serum sodium 125 m.mol/litre, serum potassium 4.6 m.mol/litre.

Blood group: A Rhesus negative.

Quantitative Paul-Bunnell Test: unabsorbed serum titre 1 in 192, guinea-pig absorbed titre 1 in 192, and ox cell absorbed titre less than 1 in 12.

Direct Coombs test positive: coating antibody of non-IgG type.

Chest X-Ray and electrocardiogram: normal.

The cold agglutinin titres are shown in Table 1.

The clinical findings and investigations established the diagnosis of a severe haemolytic anaemia associated with infectious mononucleosis. It was decided to withhold active treatment at first, but the haemoglobin level fell sharply over the 24 hours following admission, and he was then given a transfusion of four units of packed cells and started on oral prednisolone in a daily dosage of 40 mg. There was a rapid improvement in his symptoms and a return of the temperature to normal. The rise in the haemoglobin level is shown in Figure 1. No further transfusions were given and the prednisolone dosage was progressively cut down. He was discharged home on 1st June 1971 and was followed up at the Outpatients' Clinic. At his last attendance on 12th October 1971, he was well, with a normal blood picture and no evidence of haemolytic disease.

Discussion

Haemolytic anaemia in association with infectious mononucleosis was first described by Dameshek in 1943. By 1969, at least 53 patients had been reported (Worlledge and Dacie, 1969). Hoagland (1967) estimated that the incidence was 3%. Minor degrees of anaemia may be much more common (Casey and Main, 1967) but it is generally accepted that severe anaemia is rare.

Our patient's haemolytic anaemia followed the pattern described by Dacie (1960). An acute onset with high fever,

Date	*Temp*	*O R_1R_2 cells*	*O cord cells*	*Patient's cells*
2/5/71	4°C	64	64	128
	Room	16	32	8
	37°C	0	8	0
7/5/71	4°C	64	64	32
	Room	4	16	4
	37°C	0	4	0

Table 1. Cold Agglutinin titres.

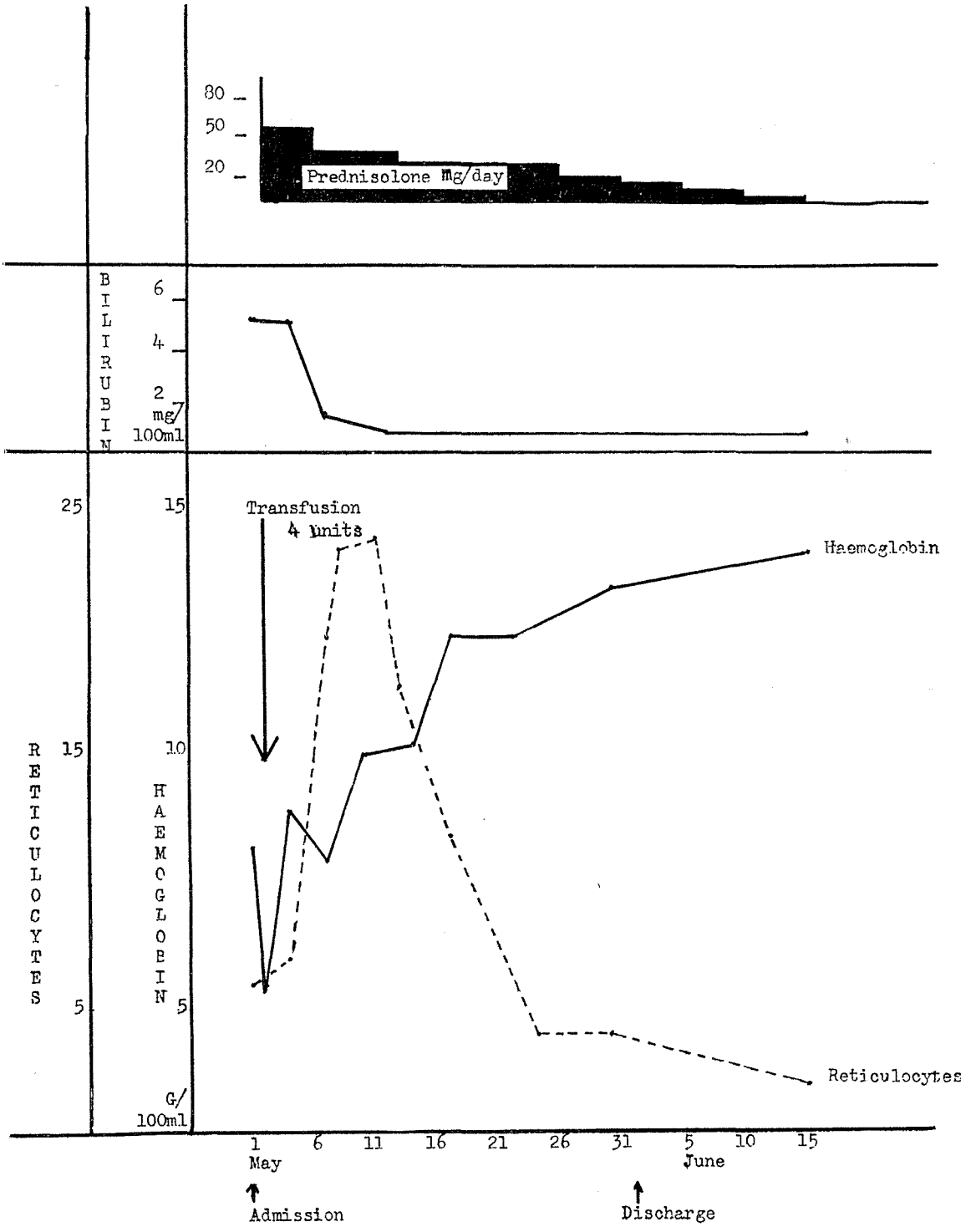
80
50
20
Prednisolone mg/day
BILIRUBIN
6
4
2
mg/
100ml
25
15
10
5
RETICULOCYTES
HAEMOGLOBIN
G/
100ml
Transfusion
4 units
Haemoglobin
Reticulocytes
1
6
11
16
21
26
31
5
10
15
May
June
Admission
Discharge

FIGURE 1

rapidly advancing anaemia and jaundice is characteristic. The anaemia usually appears one to two weeks after the onset of symptoms of infectious mononucleosis, but both may develop simultaneously in a quarter of cases, as occurred in our patient. Haemoglobinuria is uncommon, but has been reported in at least four cases (Dacie, 1960). The severity of the haemolysis may be of any degree, and spherocytosis is a frequent feature. The rise in the reticulocyte count may be surprisingly small in the early stages, possibly reflecting a temporary functional or actual bone marrow hypoplasia (Mengel *et al.*, 1964). The prognosis is excellent as the haemolysis is characteristically transient, subsiding spontaneously in one or two months, unless there is an associated hereditary haemolytic disease such as thalassaemia (Thurm and Bassen, 1955). Recovery may be hastened by keeping the patient warm. Blood transfusion is only required in the more severe cases, and difficulty in grouping is not usually met provided all procedures are carried out at 37°C. No untoward reactions followed transfusion in our patient. Corticosteroids are of uncertain value, but difficult to withhold in a seriously ill patient. The symptomatic improvement with prednisone therapy in our patient was almost certainly unrelated to any effect on the haemolysis.

The evidence now available suggests that the increased red cell destruction in infectious mononucleosis is commonly due to an auto-antibody of i-specificity. The first cases of anaemia due to anti-i antibodies were described by Calvo *et al.* (1965) and Jenkins *et al.* (1955). Most cases that have been studied since then have shown an association with anti-i antibodies, but hypersplenism, inherited red cell defects aggravated by the disease and as yet unidentified metabolic toxins (Keyloun and Grace, 1966) have been held responsible in rare instances. It is now realised that the commonest cause of anti-i haemolytic anaemia in temperate climates is infectious mononucleosis, though it has been reported in occasional patients with lymphoma, terminal malignancy and alcoholic cirrhosis (Rubin and Solomon, 1967). In tropical countries anti-i haemolytic anaemia is a frequent feature of the "tropical splenomegaly" syndrome.

Recent studies have established that anti-i antibody is commonly produced in infectious mononucleosis even in the absence of haemolytic anaemia. Jenkins (1965) found evidence of anti-i in 8% of his patients, but several reports have suggested a much higher incidence up to 71% (Rosenfield *et al.*, 1965). It seems likely that the causative organism of infectious mononucleosis commonly stimulates the production of anti-i antibodies as a transient phenomenon during the phase of maximal reticulo-endothelial hyperplasia, at a time when a number of transient 'false positive' immunological reactions (such as the Wassermann reaction) may also be demonstrated (Carter, 1966).

The anti-i antibody apparently gives rise to detectable haemolytic disease in only a small proportion of cases. It is believed that one important factor may be the thermal amplitude of the antibody, haemolysis only occurring in those cases where activity is retained at room temperature. Why anti-i should ever produce haemolytic anaemia in adults is not clear. Adults with i red cells are extremely rare in temperate climates. Jenkins (1960) could not find a single example among 17,000 British blood donors. It is true that five of the reported cases of infectious mononucleosis with haemolytic anaemia due to anti-i also had hereditary red cell defects — spherocytosis and thalassaemia — known to result in increased agglutination with anti-i (Gilbert and Crookston, 1964), but in the majority of cases this was not the case. A possible explanation may be a temporary disturbance in the ratio of I and i antigens in red cells produced during the early phases of infectious mononucleosis. Similar disturbances are known to occur in conditions where red cells are prematurely released from the bone marrow.

It is of great interest that our patient did not show evidence of anti-i antibody activity. The haemolytic anaemia was associated with cold agglutinins which

agglutinated adult O red cells and cord O red cells to the same high titre at 5°C and to a lesser titre at 28°C. Further investigation revealed that the antibody had an anti-HI specificity. This antibody may have some similarities with the one described by Brafield (1966) in his patient with infectious mononucleosis, which agglutinated both I and i cells to the same high titre at 4°C, but was present still a year later, casting some doubt on its significance in the aetiology of the anaemia. In our patient however the antibody titres fell within four weeks and no abnormal agglutinins could be detected four months later. We therefore believe that the haemolytic anaemia in our patient was due to an auto-antibody of HI-specificity not previously described in infectious mononucleosis.

Acknowledgements:

I wish to thank Dr. K. F. R. Schiller of St. Peter's Hospital, Chertsey, Surrey, for permission to publish this case and encouragement to write this paper, as well as Dr. R. Vaughan Jones and Mrs. D. Hicks of the North West Surrey Group Laboratory and the South London Blood Transfusion Centre for their help.

References

BRAFIELD A.J. (1966) Lancet, i, 982

CALVO R., STEIN W., KOCHWA S., and ROSENFIELD R.E. (1965), J. Clin. Invest., *44*, 1033

CARTER R.L. (1966) Br. J. Haemat. *12*, 268

CASEY T.P. and MAIN B.W. (1967) N.Z med. J. *66*, 664

DACIE J.V. (1962) The Haemolytic Anaemias: Congenital and Acquired. Part II. The Auto-immune Haemolytic Anaemias. (Churchill)

DAMESHEK W. (1943) J. Am. med. Ass., *123*, 77

GIBLETT E.R. and CROOKSTON M.C. (1964) Nature, *201*, 1138.

HOAGLAND R.J. (1967) Infectious mononucleosis. (Grune and Stratton)

JENKINS W.J., MARSH W.L., KOSTER H.G., and CARTER R.L. (1965) Brit. J. Haemat. *11*, 480.

JENKINS W.J., MARSH W.L., NOADES J., TIPPETT P., SANGER R., and RACE R.R. (1960) Lancet, i, 1158.

KEYLOUN V.E. and GRACE W.J. (1966) N.Y. St. J. Med. *66*, 273.

MENGEL C.E., WALLACE A.G., and MCDANIEL A.G. (1964) Arch. Int. Med., *114*, 333.

PITNEY W.R., THOMAS H.N., and WELLIS J.V. (1968) Vox sang. *14*, 438

RUBIN H. and SOLOMON A. (1967) Vox sang. *12*, 227

ROSENFIELD R.E., SCHMIDT P.J., CALVO R.C. and MCGINNISS M.H. (1965) Vox. sang. *10*, 631

THURM R.H. and BASSEN F. (1955), Blood, *10*, 841

WORLLEDGE S.M. and DACIE J.V. (1969) Infectious mononucleosis. (Blackwell)